Notes

3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 4.[1] Side Chain Ester Derivatives of Mevinolin

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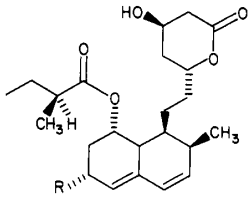
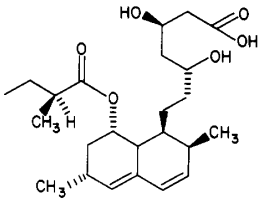
Modification of the 2(*S*)-methylbutyryl moiety of mevinolin led to a series of side chain ester derivatives. A systematic exploration of the structure–activity relationships showed that the introduction of an additional aliphatic group on the carbon α to the carbonyl group increased potency. This observation led to the synthesis of compound **16**, which has about 2.5 times the intrinsic inhibitory activity of mevinolin.

The novel fungal metabolites compactin (ML-236B)[2,3] (**1a**) and mevinolin (MK-803, monacolin K)[4,5] (**1b**) are potent inhibitors of cholesterol biosynthesis at the level of the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMG-CoA reductase; mevalonate:NADP$^+$ oxidoreductase (CoA acylating), EC 1.1.1.34].[6] Mevinolinic acid (**2**), the dihydroxy acid form of the lactone **1b**, is the most potent inhibitor (K_i = 0.6 nM)[4] reported to date and is an effective hypocholesterolemic agent in several animal species and man.[4,7] Since HMG-CoA reductase[6] catalyses the rate-limiting step in cholesterogenesis and hypercholesterolemia is a known primary risk factor[8,9] for coronary heart disease (the major cause of death in Western countries), it was deemed important to delineate the structural features of mevinolin responsible for its HMG-CoA reductase inhibitory activity. In this paper, the first of a series describing studies on the structural modification of mevinolin, we describe the results of modifying the 2(*S*)-methylbutyryl moiety, some of which led to side chain ester derivatives with enhanced potencies.



1a, R = H
b, R = CH_3



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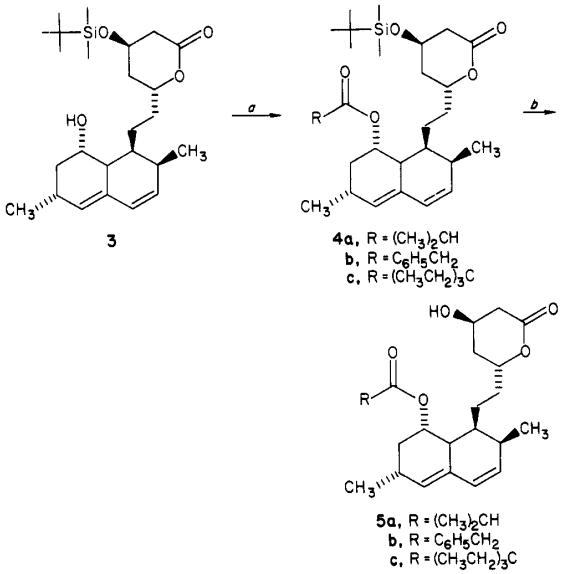
Chemistry. The compounds prepared for this study are listed in Table I. Their syntheses from the corresponding silyl ether **3**[10] are shown in Scheme I. Acylation of the hindered axial alcohol **3** with isobutyryl chloride in pyridine containing 4-(dimethylamino)pyridine (DMAP)

Scheme I



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4a, R = $(CH_3)_2CH$
b, R = $C_6H_5CH_2$
c, R = $(CH_3CH_2)_3C$

5a, R = $(CH_3)_2CH$
b, R = $C_6H_5CH_2$
c, R = $(CH_3CH_2)_3C$

[a] **4a** (method A): $(CH_3)_2CHCOCl$, 4-DMAP, pyridine, 20 °C, 18 h. **4b** (method B): $PhCH_2CO_2H$, dicyclohexylcarbodiimide, 4-pyrrolidinopyridine, CH_2Cl_2, 20 °C, 18 h. **4c** (method C): $(CH_3CH_2)_3CCOCl$, 4-pyrrolidinopyridine, pyridine, 100 °C, 12 h. [b] Three equivalents of $Bu_4N^+F^-\cdot 3H_2O$, 4 equiv of HOAc, THF, 20 °C, 18 h.

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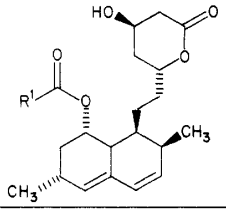
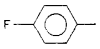
(1) Part 3: Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170.
(2) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(3) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.
(4) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.
(5) Endo, A. *J. Antibiot.* **1980**, *33*, 334.
(6) Rodwell, V. W.; Nordstrom, J. L.; Mitschelen, J. J. *Adv. Lipid Res.* **1976**, *14*, 1.
(7) (a) Tobert, J. A.; Hitzenberger, G.; Kukovetz, W. R.; Holmes, I. B.; Jones, K. H. *Atherosclerosis* **1982**, *41*, 61. (b) Tobert, J. A.; Bell, G. D.; Birtwell, J.; James, I.; Kukovetz, W. R.; Pryor, J. S.; Buntinx, A.; Holmes, I. B.; Chao, Y.-S.; Bolognese, J. A. *J. Clin. Invest.* **1982**, *69*, 913.
(8) Kannel, W. B.; Castelli, W. P.; Gordon, T.; McNamara, P. M. *Ann. Intern. Med.* **1971**, *74*, 1.
(9) Stamler J. *Arch. Surg.* **1978**, *113*, 21.

Table I. Effects of Modification of the Side Chain Ester Moiety of Mevinolin



no.	R^1	recryst solvent	mp, °C	formula[a]	method[b]	IC_{50},[c] nM	relative potency[d]
1b						2.2	254
6	CH_3	n-C_4H_9Cl	153–156	$C_{21}H_{30}O_5 \cdot 0.1C_4H_9Cl$	A	269	2.1
7		ether/hexane	116–119	$C_{23}H_{32}O_5$	B	38.6	14
8	$CH_3(CH_2)_3$	chromat CH_2Cl_2/acetone (4/1)	semisolid	$C_{24}H_{36}O_5$	A	8.7	64
9	$CH_3(CH_2)_8$	chromat CH_2Cl_2/acetone (9/1)	semisolid	$C_{29}H_{46}O_5$	B	295	1.9
5a	$(CH_3)_2CH$	CH_3CN/H_2O	144–147	$C_{23}H_{34}O_5$	A	7.7	72
10	$(CH_3)_2CHCH_2$	ether	119–123	$C_{24}H_{36}O_5$	A	5.4	103
11	$(CH_3)_2C{=}CH$	prep HPLC Zorbax ODS CH_3CN/H_2O (45/55)	113–118	$C_{24}H_{34}O_5$[e]	B	27.3	20
12	$CH_2{=}C(CH_3)CH_2$	prep HPLC Zorbax ODS CH_3CN/H_2O (45/55)	116–119	$C_{24}H_{34}O_5$[e]	B	2.9	187
13	$CF_3CH(CH_3)CH_2$	chromat CH_2Cl_2/acetone (4/1)	110–113	$C_{24}H_{33}F_3O_5$	B	3.5	157
14		prep HPLC Altex C_8 CH_3CN/H_2O (45/55)	126–128	$C_{24}H_{36}O_5$	A	2.2	254
15	$(CH_3)_3C$	n-C_4H_9Cl	167.5–170.5	$C_{24}H_{36}O_5$	A	2.7	209
16	$C_2H_5C(CH_3)_2$	n-C_4H_9Cl/hexane	135–138	$C_{25}H_{38}O_5$	C[f]	0.9	622
17	$(C_2H_5)_2C(CH_3)$	n-C_4H_9Cl/hexane	111–113	$C_{26}H_{40}O_5$	C	1.4	394
5c	$(C_2H_5)_3C$	CH_3CN/H_2O	129–132	$C_{27}H_{42}O_5$	C	1.4	391
18	$C_3H_7C(C_2H_5)_2$	ether/hexane	81–83	$C_{28}H_{44}O_5$	C	1.9	294
19		cyclohexane	155–158	$C_{30}H_{42}O_5 \cdot {}^1/_{20}C_6H_{12}$	A[g]	3.8	147
20		chromat ether/CH_2Cl_2 (1/1)	119.5–120.5	$C_{26}H_{31}FO_5$	A	37	15
5b		CH_3CN/H_2O	109–112	$C_{27}H_{34}O_5$	B	19	29
21		n-C_4H_9Cl	120–122	$C_{26}H_{32}O_6 \cdot {}^1/_4C_4H_9Cl$	A	83	6.8

[a] Analytical results are within ±0.4% of the theoretical values. [b] See Experimental Section for details of methods A–C. [c] See Experimental Section for protocol. [d] For estimation of relative inhibitory potencies, compactin was assigned a value of 100 and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. [e] C, H analysis was not obtained. The 360-,Hz NMR was in full agreement with the structure. [f] The acylation was run at 100 °C for 4 h. [g] The acylation was run at ambient temperature for 5 days.

as a catalyst at ambient temperature for 18 h (method A) resulted in quantitative conversion to the ester **4a**. An alternative acylation procedure (method B) is demonstrated by the preparation of the phenylacetic ester **4b** via treatment of a CH_2Cl_2 solution of the alcohol **3** with phenylacetic acid and dicyclohexylcarbodiimide in the presence of 4-pyrrolidinopyridine. This procedure was also used for the preparation of **7**, since the attempted synthesis of **7** by method A failed to provide any of the desired ester. However, method B could not be used to prepare the adamantyl derivative **19** as no acylation occurred after 3 days. The extremely hindered esters such as the diethylbutyric ester **4c** could not be prepared by methods A or B but required more vigorous acylation conditions. Heating a pyridine solution of the alcohol **3** and the diethylbutyryl chloride at 100 °C for 12 h in the presence of DMAP or 4-pyrrolidinopyridine as a catalyst provided the ester **4c** (method C). In this instance, the overall yield was only 40% because of byproducts resulting from the elimination of the β-silyloxy ether at elevated temperatures.

As noted previously,[10] attempted deprotection of the silyl ethers **4** with tetrabutylammonium fluoride in THF caused rapid and extensive destruction of the lactone ring.[11] Attenuation of the offending basicity of fluoride by addition of acetic acid permitted clean unmasking of the β-hydroxy lactones **5**.

Biological Results and Discussion

The compounds listed in Table I were converted to their ring-opened sodium dihydroxy carboxylate salts and were evaluated for their ability to inhibit solubilized, purified rat liver HMG-CoA reductase. The elimination of branching in the side chain ester moiety of **1b** provided compounds **6–9**, which had diminished inhibitory activities. The removal of the terminal methyl from the 2-methylbutyryl moiety gave **5a**, which was about one-third as

(10) Willard, A. K.; Smith, R. L. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 337.

(11) Treatment of mevinolin (**1b**) under the same reaction conditions (i.e., 3 equiv of $Bu_4N^+F^- \cdot 3H_2O$, THF, 20 °C) for 2 h followed by careful acidification (1 N HCl, slight excess) afforded mevinolinic acid (**2**) *exclusively*. Hence, although both β-silyloxy lactones **4** and β-hydroxy lactone **1** are sensitive to the basicity of fluoride under typical Corey conditions,[14] their relative propensities toward 1,2-diaxial elimination differ markedly.

potent as **1b**. When the α-methyl group was moved further from the carbonyl group (i.e., to the β-carbon (**10**)), activity was diminished by 50%. The introduction of unsaturation into the isopentyl moiety of **10** to provide **11** lowered the intrinsic inhibitory activity. However, when the double bond was moved to the β and γ carbons, activity was increased. Replacing the terminal methyl of **10** with a trifluoromethyl group **13** also increased the activity. Interestingly, stereochemistry at the carbon α to the carbonyl group is not critical as **1b** and its diastereomer **14** are equally potent. The introduction of an additional methyl group on the carbon α to the carbonyl group to give **16** increased the potency about 2.5-fold. Increasing the length of the substituents on the α carbon provided esters **17**, **5c**, and **18**, which were less potent than **16** but more potent than **1b**. Replacement of the bulky side chain of **16** with the more compact adamantyl moiety (**19**) ablated activity as did conversion to aromatic esters **20**, **5b**, and **21**. No statistically significant correlation could be made between log P[12] or volume[13] and log (relative potency) for the 20 side chain ester derivatives in Table I.

Analysis of the intrinsic inhibitory activities of these compounds suggests the following: (a) the stereochemistry of the side chain ester moiety is not important for inhibitory binding to HMG-CoA reductase; (b) the spacial requirements of the acyl moiety are compatible with compact, branched-chain aliphatic acyl groups; and (c) additional branching at the α carbon of the acyl moiety increases potency. Further modifications of the side chain ester moiety as well as other portions of the mevinolin structure along with in vivo testing results will be described in subsequent papers from these laboratories.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were recorded in $CDCl_3$, unless noted otherwise, on either a Varian EM-390, XL-300, or NT-360 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analysis for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. All starting materials were commercially available unless indicated otherwise.

[1*S*-[1α,3α,7β,8β(2*S,4*S**)8aβ]]-8-[2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]tetrahydro-6-oxo-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-1-naphthalenyl 2-Methylpropionate (4a) (Method A).** Isobutyl chloride (0.49 g, 4.6 mmol) was added over 2 min to a stirred solution of the alcohol **3**[10] (0.5 g, 1.15 mmol) and DMAP (50 mg) in dry pyridine (5 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 18 h. The reaction mixture was diluted with ether (100 mL) and washed with 2% aqueous HCl (3 × 25 mL), saturated $NaHCO_3$ solution (25 mL), and brine (2 × 25 mL). After drying ($MgSO_4$) and filtration, the solution was evaporated to give crude **4a** as a viscous yellow oil. The oil was chromatographed on a silica gel (230–400 mesh) column. Elution with CH_2Cl_2–acetone (32.3:1, v/v, 200 mL) provided a forerun, which was discarded. Continued elution with the same eluant (200 mL) gave the ester **4a** (0.58 g) as a pale yellow oil. NMR δ 0.09 (6 H, s), 0.88 (9 H, s), 1.13 (6 H, d, J = 6 Hz), 4.32 (H, m), 4.63 (H, m), 5.34 (H, m), 5.54 (H, m), 5.78 (H, dd, J = 6, 10 Hz), 6.03 (H, d, J = 10 Hz).

[1*S*-[1α,3α,7β,8β(2*S,4*S**),8aβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-Methylpropionate (5a).** A solution of **4a** (0.58 g, 1.15 mmol) in THF (10 mL) was added to a magnetically stirred solution of acetic acid (0.341 g, 4.8 mmol) and $Bu_4N^+F^-\cdot 3H_2O$ (1.13 g, 3.6 mmol) in THF (10 mL), and the reaction was stirred 18 h at ambient temperature. The reaction mixture was diluted with ether (100 mL) and washed successively with 2% aqueous HCl, H_2O (25 mL), and brine (2 × 25 mL). After drying ($MgSO_4$) and filtration, the solution was evaporated to provide **5a** as a pale yellow solid. The solid was chromatographed on a silica gel (230–400 mesh) column. Elution with CH_2Cl_2–acetone (4:1, v/v, 300 mL) provided a forerun, which was discarded. Continued elution with the same eluant (280 mL) gave the ester **5a**. Recrystallization of the solid provided an analytical sample as colorless needles. NMR δ 0.88 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 1.13 (6 H, d, J = 6 Hz), 2.67 (2 H, m), 4.30 (H, m), 4.55 (H, m), 5.30 (H, m), 5.50 (H, m), 5.70 (H, dd, J = 6, 10 Hz), 5.95 (H, d, J = 10 Hz).

[1*S*-[1α,3α,7β,8β(2*S,4*S**),8aβ]]-8-[2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]tetrahydro-6-oxo-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-1-naphthalenyl Benzeneacetate (4b) (Method B).** A solution of the alcohol **3** (434 mg, 1.0 mmol), benzeneacetic acid (204 mg, 1.5 mmol) and *N,N'*-dicyclohexylcarbodiimide (309 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was treated with 4-pyrrolidinopyridine (22 mg, 0.15 mmol) and stirred at ambient temperature under a nitrogen atmosphere. After 3 days the solvent was removed in vacuo and the residue was suspended in ether (25 mL) and filtered. Evaporation of the filtrate provided a viscous oil, which was chromatographed on silica gel (230–400 mesh). Elution with ether–hexane (1:1, v/v, 60 mL) gave a forerun, which was discarded. Continued elution with the same eluant (60 mL) provided the ester **4b** as a colorless, viscous oil (460 mg, 83%). NMR δ 0.10 (6 H, s), 0.90 (9 H, s), 3.58 (2 H, s), 4.23 (H, m), 4.43 (H, m), 5.34 (H, m), 5.57 (H, m), 5.77 (H, dd, J = 6, 10 Hz), 6.03 (H, d, J = 10 Hz), 7.30 (5 H, br s).

[1*S*-[1α,3α,7β,8β(2*S,4*S**),8aβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl Benzeneacetate (5b).** This product was prepared analogously to **5a**, starting with **4b** (460 mg, 0.83 mmol) and purified by chromatography and recrystallization. NMR δ 0.83 (3 H, d, J = 7 Hz), 1.04 (3 H, d, J = 7 Hz), 3.58 (2 H, s), 4.10–4.60 (2 H, br m), 5.36 (H, m), 5.57 (H, m), 5.78 (H, dd, J = 6, 10 Hz), 6.03 (H, d, J = 10 Hz), 7.33 (5 H, br s).

[1*S*-[1α,3α,7β,8β(2*S,4*S**),8aβ]]-8-[2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]tetrahydro-6-oxo-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-1-naphthalenyl 2,2-Diethylbutanoate (4c) (Method C).** 2,2-Diethylbutyryl chloride (18.8 g, 115 mmol) was added to a magnetically stirred solution of the alcohol **3** (12.5 g, 28.7 mmol) and 4-pyrrolidinopyridine (0.425 g, 2.87 mmol) in dry pyridine (100 mL), heated at 100 °C. The solution was stirred under a N_2 atmosphere for 12 h, cooled to ambient temperature, and added to ether (300 mL). The ethereal mixture was washed with 3 N HCl (3 × 100 mL) and brine (4 × 100 mL) and dried ($MgSO_4$). After filtration and evaporation the crude product was chromatographed on a column of silica gel (70–230 mesh, 1 kg). Elution with ether–hexane (1:1, v/v, 3500 mL) provided a forerun, which was discarded. Continued elution with the same eluant gave the ester **4c** as a yellow oil (6.5 g, 40%). NMR δ 0.08 (6 H, s), 0.90 (9 H, s), 2.59 (2 H, d, J = 4 Hz), 4.32 (H, m), 4.63 (H, m), 5.52 (2 H, m), 5.80 (H, dd, J = 6, 10 Hz), 6.07 (H, d, J = 10 Hz).

[1*S*-[1α,3α,7β,8β(2*S,4*S**),8aβ]]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2,2-Diethylbutyrate (5c).** This compound was prepared analogously to **5a**, starting with **4c** (6.4 g, 11.5 mmol) and purified by chromatography and recrystallization. NMR δ 0.76 (9 H, t, J = 7 Hz), 0.83 (3 H, d, J = 7 Hz), 1.09 (3 H, d, J = 7 Hz), 4.38 (H, m), 4.61 (H, m), 5.49 (2 H, m), 5.79 (H, dd, J = 10, 7 Hz), 6.00 (H, d, J = 10 Hz).

2,2-Diethylpentanoic acid (22) was prepared by the general method of Pfeffer et al.[15] *n*-Propyl bromide (5.4 g, 0.044 mol) was rapidly added at 0 °C to the dianion of 2-ethylbutanoic acid (5.1 g, 0.044 mol) prepared in THF solution, and the reaction was stirred for 3 h at ambient temperature. Neutralization of the

(12) Smith, G. M., in house program.
(13) Pomona Medchem Project, Pomona College, Claremont, CA.
(14) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(15) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451.

reaction by the addition of 10% HCl (100 mL) at 0 °C gave a mixture, which was extracted into petroleum ether (2 × 250 mL). The organic extracts were combined, washed with saturated brine (4 × 50 mL), dried ($MgSO_4$), and evaporated to provide a liquid (7.4 g), which was distilled to give **22**; bp 133–134 °C (20 mm) (5.2 g, 75%). NMR δ 0.70–1.00 (9 H, m), 1.03–1.37 (2 H, m), 1.40–1.77 (6 H, m).

The following acid chlorides were prepared by heating the acid and 2 equiv of thionyl chloride at 100 °C for 2 h and purified by distillation.

2,2-Dimethylbutyryl chloride: bp 130–134 °C; yield 76%; NMR δ 0.83 (3 H, t, J = 7 Hz), 1.20 (6 H, s), 1.60 (2 H, q, J = 7 Hz).

2-Ethyl-2-methylbutyryl chloride: bp 155–158 °C; yield 61%; NMR δ 0.90 (6 H, t, J = 7 Hz), 1.20 (3 H, s), 1.43–1.97 (4 H, m).

2,2-Diethylbutyryl chloride: bp 65–66 °C (20 mm); yield 90%; NMR δ 0.83 (9 H, t, J = 7 Hz), 1.70 (6 H, t, J = 7 Hz).

2,2-Diethylpentanoyl chloride: bp 80–81 °C (20 mm); yield 92%; NMR 0.73–1.00 (9 H, m), 1.10–1.43 (2 H, m), 1.53–1.87 (6 H, m).

Isolation of HMG-CoA reductase was carried out as previously described.[16]

HMG-CoA Reductase Inhibition Assay. IC_{50} values were determined with use of five levels of each inhibitor in the assay slightly modified from that previously described.[4] In the revised protocol, enzyme was incubated for 5 min with inhibitor and NADPH prior to initiating the reaction with [^{14}C]HMG-CoA (12.5 μM, 5.9 μCi/μmol). IC_{50} values were calculated from percent inhibitions.

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(16) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.

3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 5. 6-(Fluoren-9-yl)- and 6-(Fluoren-9-ylidenyl)-3,5-dihydroxyhexanoic Acids and Their Lactone Derivatives

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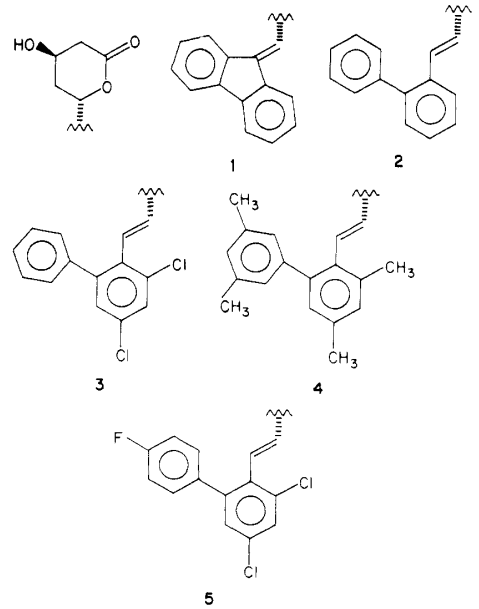
A limited study was conducted to determine the biological consequences of rendering the phenyl rings of the previously reported[1] 7-(3,5-disubstituted [1,1′-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic acids coplanar. Such constraint substantially diminished intrinsic HMG-CoA reductase inhibitory activity.

In a previous paper[1] on HMG-CoA reductase inhibitors, we reported the syntheses and biological properties of a series of 7-(3,5-disubstituted [1,1′-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic (and heptanoic) acids and their δ-lactones. In this paper, we describe the syntheses and biological consequences of rendering the two phenyl groups of the 1,1′-biphenyl fragment coplanar. The rationale for such a study is the observation that the intrinsic HMG-CoA reductase inhibitory potency of unsubstituted fluorenylidene **1** (from part 1)[2] is slightly greater than that of unsubstituted biphenyl **2** (from part 2).[3] From those substituted biphenyl compounds in part 3 of this series,[1] compounds **3–5** were chosen for determining the effects of these constraints. The inherent difficulty in elaborating the dichlorofluorenylidene compound corresponding to biphenyl **3** compelled us to prepare the analogous dimethyl compound (**8**). We showed previously[1,3] that analogous methyl-for-chlorine replacement on the central phenyl ring produces little, if any, lowering of intrinsic inhibitory potency.



[†] Merck Sharp & Dohme, West Point, PA.
[‡] Merck Sharp & Dohme, Rahway, NJ.

(1) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J. Jr.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170.
(2) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.
(3) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 159.

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